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**EUROPEAN PATENT APPLICATION**

(21) Application number: 85301868.7

(51) Int. Cl.<sup>4</sup>: **C 07 D 307/935**  
**C 07 C 177/00**

(22) Date of filing: 18.03.85

(30) Priority: 19.03.84 JP 51058/84

(43) Date of publication of application:  
02.10.85 Bulletin 85/40

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

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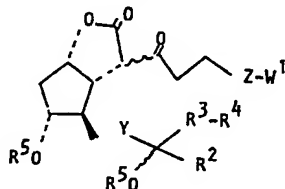
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(54) Intermediates for the preparation of prostaglandin analogues.

(57) The present invention relates to intermediates of the general formula:



groups R<sup>5</sup>, which may be the same or different, each represents an alkyl group of 1 to 4 carbon atoms, a phenyl group or an aralkyl group of 7 to 12 carbon atoms or R<sup>7</sup> represents an acyl group of 2 to 12 carbon atoms and R<sup>5</sup> is as hereinbefore defined) with the proviso that, when R<sup>3</sup> represents a single bond, R<sup>4</sup> does not represent a substituted or unsubstituted phenoxy group, which are useful in the preparation of 6-keto-prostaglandin derivatives.

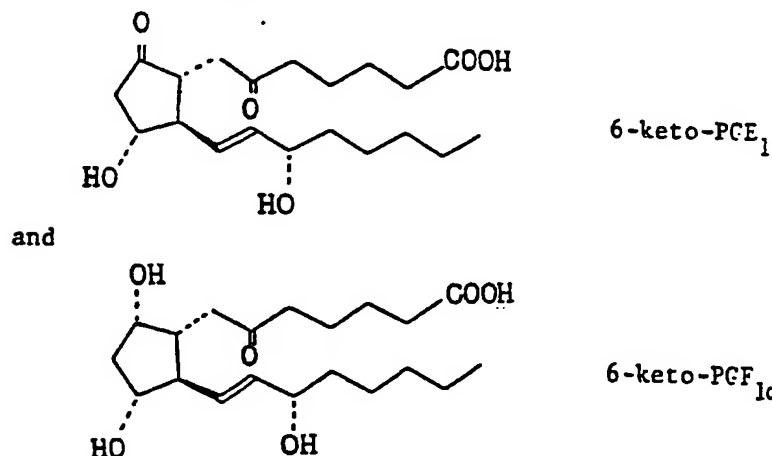
(wherein Y and Z, which may be the same or different, each represents a trans-vinylene group or an ethylene group, R<sup>1</sup> represents a hydrogen atom or a methyl or ethyl group, R<sup>2</sup> represents a single bond or an alkylene group of 1 to 5 carbon atoms, R<sup>3</sup> represents an alkyl group of 1 to 8 carbon atoms, a cycloalkyl group of 4 to 7 carbon atoms unsubstituted or substituted by at least one alkyl group of 1 to 8 carbon atoms or a phenyl or phenoxy group unsubstituted or substituted by at least one halogen atom, trifluoromethyl group of alkyl group of 1 to 4 carbon atoms, R<sup>4</sup> represents a hydroxy-protecting group which can be removed in acidic conditions and W<sup>1</sup> represents a group of the formula: -COOR<sup>1</sup>, -CON(R<sup>1</sup>)<sub>2</sub>, -CH<sub>2</sub>OR<sup>1</sup> or -CH(OR<sup>1</sup>)CH<sub>2</sub>OR<sup>1</sup> (in which R<sup>1</sup> represents a hydrogen atom or an alkyl group of 1 to 12 carbon atoms, the

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INTERMEDIATES FOR THE PREPARATION OF  
PROSTAGLANDIN ANALOGUES

This invention relates to intermediates useful in the preparation of 6-keto-prostaglandin derivatives, to a process for their preparation, and to their use.

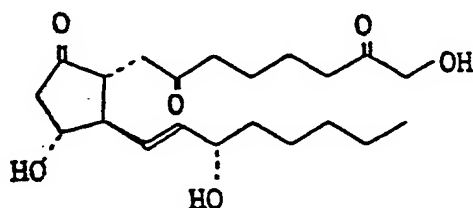
The 6-keto-prostaglandin derivatives 6-keto-PGE<sub>1</sub> and 6-keto-PGF<sub>1α</sub> are compounds of the formula:



They and their analogues possess the valuable pharmacological properties typical of the prostaglandins in a selective fashion, in particular hypotensive activity, inhibitory activity on gastric acid secretion and gastric ulceration, stimulatory activity on uterine contraction and abortifacient, luteolytic and antinidatory activity, and are useful in the treatment of hypertension, in the treatment of disorders of the peripheral circulation, in the prevention and treatment of cerebral thrombosis and myocardial infarction, in the treatment of gastric ulceration, in the termination of pregnancy and induction of labour in pregnant

female mammals, in the treatment of impaired fertility and in the control of oestrus, contraception and menstrual regulation in female mammals. (see United States Patent No. 4215142 and German Patent Specification No.2753986).

- 5           The 6-keto-PGE<sub>1</sub> derivative 2-decarboxy-2-glycoloyl-6-keto-PGE<sub>1</sub> of the formula:

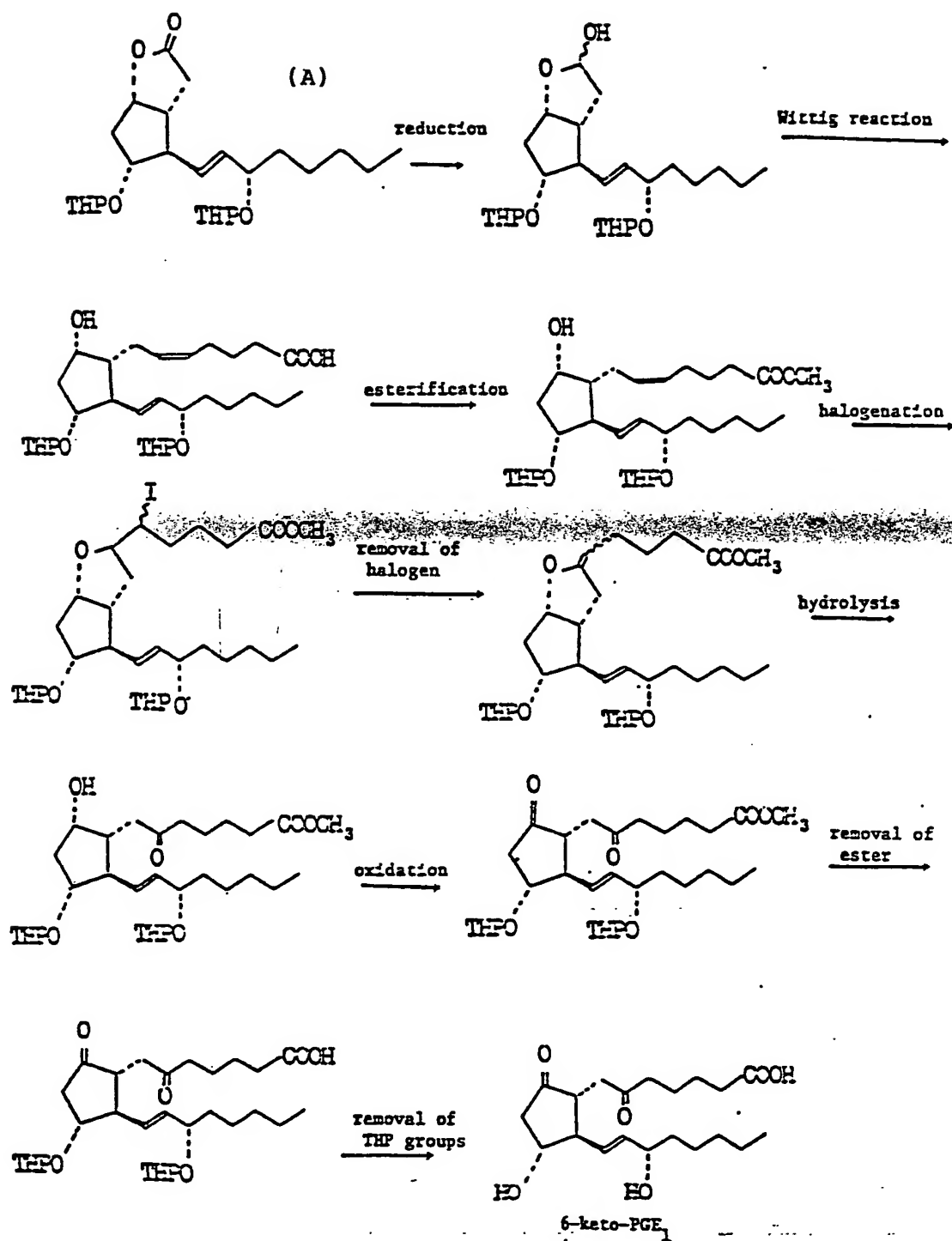


possesses selectively a strong cytoprotective activity and very low toxicity, having relatively weak pharmacological  
10 properties typical of other prostaglandins, and therefore can be used as a very effective agent for the treatment of cyto-damage (in the treatment of diseases of various organisms or systems in human beings associated with cyto-damage) (see United States Patent No.4443478).

- 15           Accordingly 6-keto-prostaglandin analogues (such as 6-keto-PGE<sub>1</sub> and 6-keto-PGF<sub>1α</sub> and their analogues which are referred to hereinafter as 6-keto-PGs) show more selective pharmacological activities associated with modified parts of the analogues' molecular skeletons and are expected  
20 to be developed as medicines in the future.

A known process for the preparation of 6-keto-PGs (see United States Patent No.4215142) is shown in Scheme A in which THP represents a tetrahydropyran-2-yl group. This known process has the disadvantage of requiring many process  
25 steps.

## Scheme A



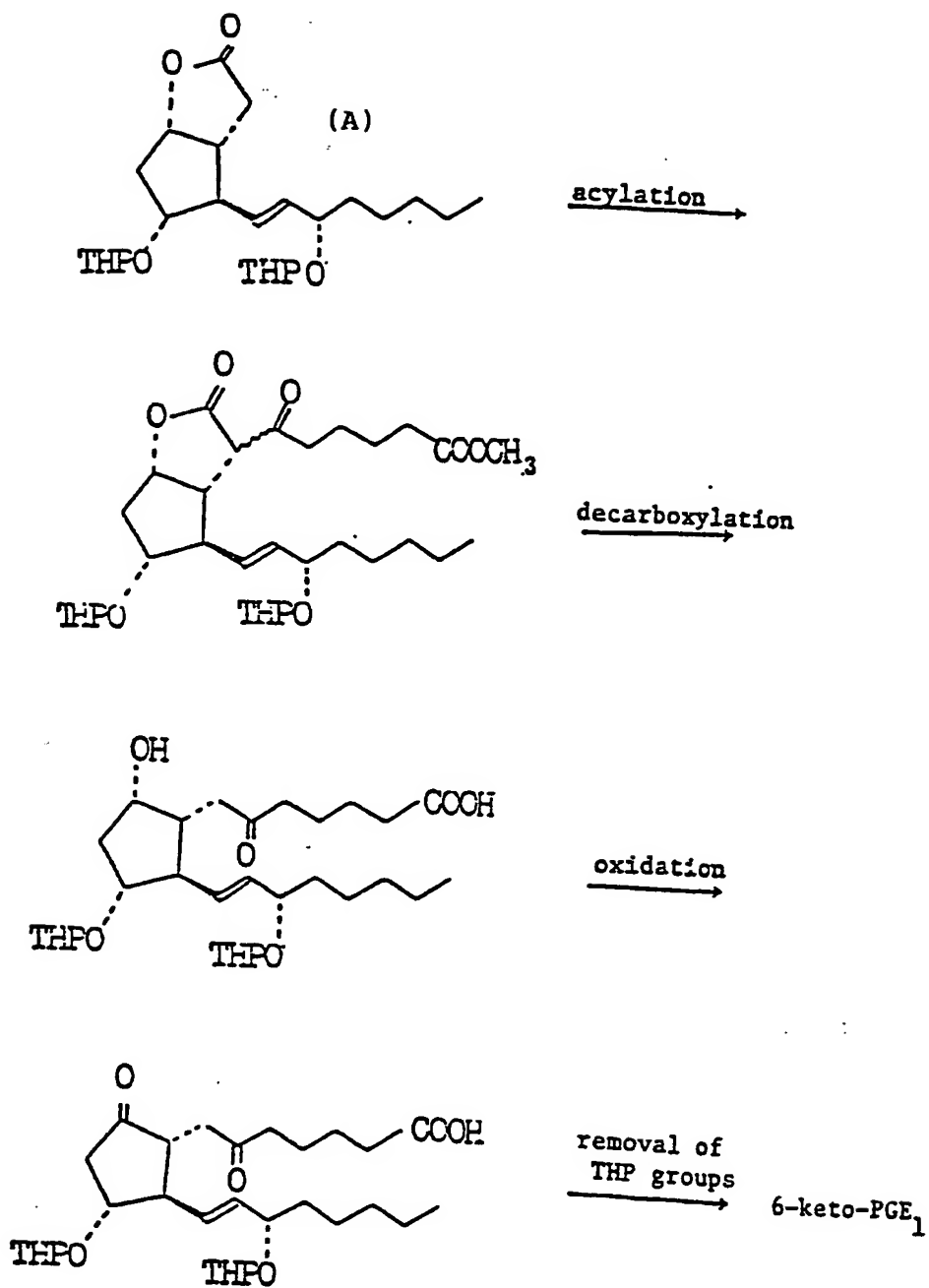
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In other known processes for the preparation of 6-keto-PGE<sub>1</sub>, the  $\alpha$ -side chain may be introduced at a different stage of the reaction sequence. However in such processes only the order of the reaction steps is changed.

5 The known process depicted in Scheme A has been chosen to provide the clearest comparison with the new preparation process using intermediates according to the present invention.

It has now been discovered that, for example,

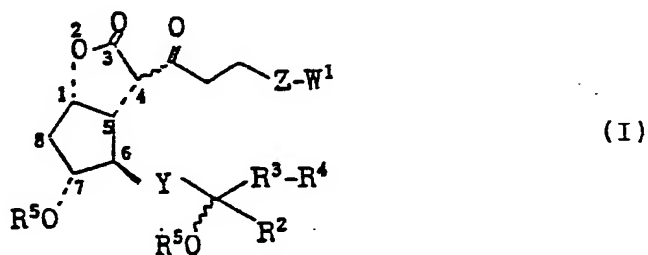
10 6-keto-PGE<sub>1</sub> may be prepared by a new sequence of reactions, via novel intermediate compounds, as shown in Scheme B, wherein THP is as hereinbefore defined.

Scheme B

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It will be seen that, starting from compound (A), the known process (Scheme A) requires 9 steps to prepare 6-keto-PGE<sub>1</sub>, whereas the process of the present invention (Scheme B) requires only 4 steps. Furthermore the reactions 5 in Scheme B such as acylation and decarboxylation are easily carried out. As a result the process of Scheme B takes less time to carry out and the overall yield is increased, leading to a corresponding reduction in overall cost.

The present invention provides compounds of the 10 general formula:



wherein Y and Z, which may be the same or different, each represents a trans-vinylene group (i.e.  $\begin{smallmatrix} H \\ \diagup \\ C = C \\ \diagdown \\ H \end{smallmatrix}$ ) or an ethylene group (i.e.  $-CH_2-CH_2-$ ), R<sup>2</sup> represents a hydrogen 15 atom or a methyl or ethyl group, R<sup>3</sup> represents a single bond or an alkylene group of 1 to 5 carbon atoms, R<sup>4</sup> represents an alkyl group of 1 to 8 carbon atoms, a cycloalkyl group of 4 to 7 carbon atoms unsubstituted or substituted by at least one alkyl group of 1 to 8 carbon 20 atoms or a phenyl or phenoxy group unsubstituted or substituted by at least one halogen atom, trifluoromethyl group or alkyl group of 1 to 4 carbon atoms, R<sup>5</sup> represents a

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hydroxy-protecting group which can be removed in acidic conditions and  $W^1$  represents a group of the formula :  $-COOR^1$ ,  $-CON(R^6)_2$ ,  $-CH_2OR^5$  or  $-CH(OR^7)CH_2OR^5$  (in which  $R^1$  represents a hydrogen atom or an alkyl group of 1 to 12 carbon atoms, the groups  $R^6$ , which may be the same or different, each represents an alkyl group of 1 to 4 carbon atoms, a phenyl group or an aralkyl group of 7 to 12 carbon atoms or  $R^7$  represents an acyl group of 2 to 12 carbon atoms and  $R^5$  is as hereinbefore defined) with the proviso that, when  $R^3$  represents a single bond,  $R^4$  does not represent a substituted or unsubstituted phenoxy group.

It is to be understood that alkyl and alkylene groups within the definitions of various symbols in this specification and the accompanying claims may be straight or branched-chain.

In the above structural formulae and in other structural formulae in this specification, the broken line (---) indicates the  $\alpha$ -configuration, the bold line (—) indicates the  $\beta$ -configuration, the wavy line (~~~~) indicates the  $\alpha$ -configuration or the  $\beta$ -configuration or a mixture thereof.

Examples of alkylene groups of 1 to 5 carbon atoms represented by  $R^3$  are methylene, ethylene, trimethylene, tetramethylene and pentamethylene groups and isomers thereof.

Examples of the alkyl groups of 1 to 8 carbon atoms represented by  $R^4$  are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl groups and isomers thereof.

Examples of the cycloalkyl groups of 4 to 7 carbon atoms unsubstituted or substituted by at least one alkyl group of 1 to 8 carbon atoms represented by  $R^4$  are cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups 5 and such groups in which one or more hydrogen atoms are replaced by alkyl groups of 1 to 8 carbon atoms named above, as examples of alkyl groups represented by  $R^4$ .

Examples of the halogen atom substituent on the phenyl or phenoxy group represented by  $R^4$  are fluorine, 10 chlorine, bromine and iodine atoms and examples of the alkyl group of 1 to 4 carbon atoms as substituents are methyl, ethyl, propyl and butyl groups and isomers thereof. Preferred groupings  $-R^3-R^4$  are, for example, n-pentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 15 4-methylpentyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,4-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, 1-propylpentyl, 2-propylpentyl, n-hexyl, 1-methylhexyl, 2-methylhexyl, 1,1-dimethylhexyl, 1-ethylhexyl, 2-ethylhexyl, n-heptyl, 2-ethylheptyl, n-nonyl, n-undecyl, cyclobutyl, 20 (1-propyl)cyclobutyl, (1-butyl)cyclobutyl, (1-pentyl)cyclobutyl, (2-propyl)cyclobutyl, (3-ethyl)cyclobutyl, (3-propyl)cyclobutyl, cyclopentyl, 1-cyclopentylethyl, 2-cyclopentylethyl, 2-cyclopentylpropyl, (2-ethyl)cyclopentyl, (2-propyl)cyclopentyl, 25 (2-butyl)cyclopentyl, (1-methyl-3-propyl)cyclopentyl, (3-butyl)cyclopentyl, (2-methyl-3-propyl)cyclopentyl, cyclohexyl, (3-ethyl)cyclohexyl, (4-methyl)cyclohexyl,

(4-ethyl)cyclohexyl, (4-propyl)cyclohexyl,  
 (2,6-dimethyl)cyclohexyl, cyclohexylmethyl,  
 (1-methyl)cyclohexylmethyl, 1-cyclohexylethyl,  
 2-cyclohexylethyl, (1-methyl-1-cyclohexyl)ethyl,  
 5 1-cycloheptylethyl, phenyl, benzyl,  $\alpha$ -phenylethyl,  
 8-phenylethyl, 1-phenylpentyl, phenoxymethyl,  
 (3-chlorophenoxy)methyl, (4-chlorophenoxy)methyl and  
 (3-trifluoromethylphenoxy)methyl: n-pentyl, 2-methylhexyl,  
 3-chlorophenoxymethyl and 3-butylcyclopentyl are especially  
 10 preferred and  $R^2$  is preferably hydrogen.

Examples of the hydroxy protecting group which can  
 be removed under acidic conditions are heterocyclic  
 groups such as tetrahydropyran-2-yl, tetrahydrofuran-2-yl  
 and tetrahydrothiopyran-2-yl groups, ether groups such as  
 15 1-ethoxyethyl, 1-methoxy-1-methylethyl, 1-methoxycyclohexyl  
 and 1-methoxy-1-phenylethyl, tri-substituted silyl groups  
 such as trimethylsilyl, triethylsilyl, tributylsilyl,  
 tert-butyldimethylsilyl, tribenzylsilyl and triphenylsilyl  
 groups and trityl group; tetrahydropyran-2-yl and  
 20 1-ethoxyethyl groups are preferred.

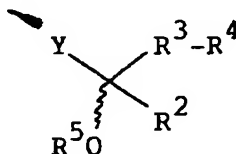
In  $W^1$  in general formula (I), examples of the alkyl  
 group of 1 to 12 carbon atoms represented by  $R^1$  in the group  
 $-COCR^1$  are methyl, ethyl, propyl, butyl, pentyl, hexyl,  
 heptyl, octyl, nonyl, decyl, undecyl and dodecyl and isomers  
 25 thereof; examples of the alkyl group of 1 to 4 carbon atoms  
 represented by  $R^6$  in the group  $-CON(R^6)_2$  are methyl, ethyl,  
 propyl and butyl and isomers thereof and examples of the

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aralkyl group of 7 to 12 carbon atoms are benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylbutyl, 4-phenylbutyl, 1-(2-naphthyl)ethyl and 2-(1-naphthyl)ethyl, and examples of the acyl group of 2 to 12 carbon atoms represented by  $R^7$  in the group  $-CH(OR^7)CH_2OR^5$  are acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, propionyl, butyryl, isobutyryl, valeryl, benzoyl and naphthylol. The groups  $COOR^1$  and  $CH(OR^7)CH_2OR^5$  are preferred.

10 Preferably  $R^1$  represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, e.g. methyl;  $R^6$  preferably represents an alkyl group of 1 to 4 carbon atoms, e.g. methyl; preferably  $R^7$  represents acetyl.

The preferred configuration of the  $OR^5$  group  
15 in the side chain is the  $\alpha$ -configuration.



The symbol Y preferably represents trans-vinylene.

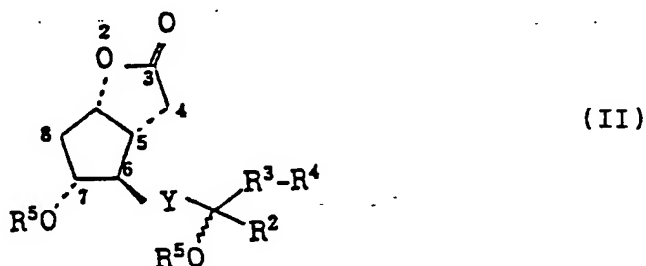
The present invention is concerned with all compounds of general formula (I) in the optically active  
20 "natural" form or its enantiomeric form or mixtures thereof, more particularly the racemic form consisting of an equimolecular mixture of the "natural" form and its enantiomeric form.

The compounds of general formula (I) have at least  
25 six asymmetric centres, i.e. the carbon atoms at the 1-, 4-, 5-, 6- and 7- positions and the carbon atom attached to the  $OR^5$  group in the side chain attached to the 6- position. When an alkyl group or an alkylene group represented by various substituents is branched-chain or when a cycloalkyl  
30 group represented by  $R^4$  is a substituted cycloalkyl group, other asymmetric centres may occur. The existence of asymmetric centres gives rise to isomerism. In the compounds of general formula (I), the substituents attached

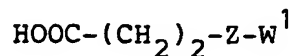
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to the carbon atoms at the 1-, 5- and 7- positions of the bicyclic skeleton (the cyclopentane ring made up of the carbon atoms at the 1-, 5-, 6-, 7- and 8- positions forms the foundation) are cis- to each other and the substituent  
 5 attached to the carbon atom at the 6- position is trans- to the substituents attached to the carbon atoms at the 1-, 5- and 7- positions. It is to be understood that all isomers and mixtures thereof as mentioned above are to be considered within the scope of general formula (I).

10 According to a feature of the present invention, compounds of the general formula (I) are prepared by acylation at the 4- position of a compound of the general formula:



15 (wherein all of the symbols are as hereinbefore defined) with a reactive derivative of a carboxylic acid of the general formula:



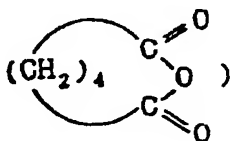
(wherein all of the symbols are as hereinbefore defined)

20 to introduce the side chain  $-\text{CO}(\text{CH}_2)_2-\text{Z}-\text{W}^1$ . The selective acylation at the 4- position of compounds of the general formula (II) may be carried out by reacting a compound of the general formula (II) with a lithium compound for example

compound of the general formula:

$$\begin{array}{c} \text{R}^8 \\ \diagdown \\ \text{NLi} \\ \diagup \\ \text{R}^9 \end{array}$$

(wherein  $\text{R}^8$  and  $\text{R}^9$ , which may be the same or different, each represents an alkyl group of 1 to 6 carbon atoms or a cycloalkyl group of 3 to 6 carbon atoms), or an alkali metal alkoxide such as sodium tert-butoxide or potassium tert-butoxide, or an alkali metal bis(trialkylsilyl)amide such as sodium bis(trimethylsilyl)amide, preferably lithium diisopropylamide (LDA), in an inert organic solvent such as toluene, tetrahydrofuran, hexane, pentane or diethyl ether, preferably in toluene, at a temperature from  $-78^\circ\text{C}$  to room temperature, preferably from  $-78^\circ\text{C}$  to  $-30^\circ\text{C}$ ; the reaction with the reactive derivative is also carried out at a temperature from  $-78^\circ\text{C}$  to room temperature. Examples of the reactive acidic derivatives are the acid halide (preferably an acid chloride), acid anhydride (an internal acid anhydride is included when  $\text{W}^1$  represents the formula  $-\text{COOH}$ , e.g.



or a diester compound (in which  $\text{W}^1$  represents  $-\text{COOR}^1$  and  $\text{R}^1$  is other than hydrogen), or a mixed acid anhydride with, for example, tert-butylchloroformate.

The starting materials of general formula (II) may be prepared by the methods described in the following literature references and patent specifications, or obvious modifications thereof:

(A) when  $\text{R}^3-\text{R}^4$  represents a straight or branched chain alkyl

- group, by the method described in United States Patent No. 4061865, British Patent No. 1398291 and Japanese Patent Publication Nos. 49-124048 and 50-101340; when  $R^3-R^4$  represents an n-pentyl group, they are obtained by the method described in J. Am. Chem. Soc., 92 397 (1970);
- 5 (B) when  $R^3$  represents a single bond or a straight or branched chain alkylene group and  $R^4$  represents a substituted or unsubstituted cycloalkyl group, they are obtained by the method described in United States Patent
- 10 Nos. 3966792, 4045468, 4061865 and 4117119 and Japanese Patent Publication Nos. 50-148339 and 53-25544;
- (C) when  $R^3$  represents a single bond or a straight or branched chain alkylene group and  $R^4$  represents a substituted or unsubstituted phenyl group, they are
- 15 obtained by the method described in United States Patent No. 4061865;
- (D) when  $R^3$  represents a straight or branched chain alkylene group and  $R^4$  represents a substituted or unsubstituted phenoxy group, they are
- 20 obtained by the method described in United States Patent No. 4065632 and Japanese Patent No. 1214209 .

The reactive carboxylic acid derivatives used in the acylation reaction can be purchased or can be prepared by known methods.

- 25 According to a feature of the present invention the intermediates of general formula (I) of the present invention may be converted into the 6-keto-PGs of the general

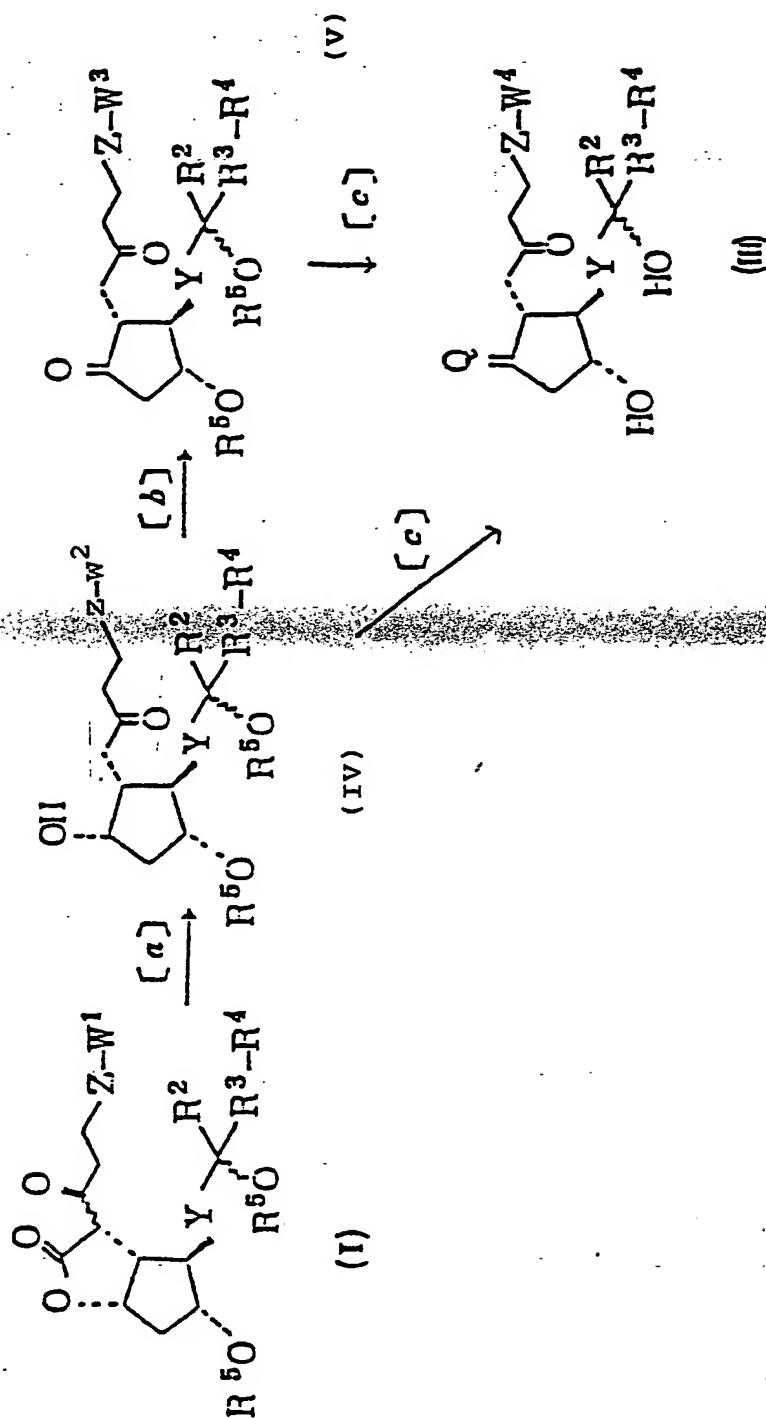
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formula (III) hereinafter described by the series of reactions depicted schematically below in Scheme C.

The configuration of the asymmetric carbon at the 4- position of the bicyclic compound of general formula (I) 5 is R-configuration, S-configuration or a mixture thereof, but the asymmetric carbon disappears by decarboxylation in the step [a] and therefore the final products are not related to the asymmetric carbon atom at the 4-position.

The hydroxy-protecting groups R<sup>5</sup> in the compounds 10 of the present invention, which are removed by hydrolysis in step [c] of Scheme C, are groups which can be removed under acidic conditions without affecting other parts of the molecule.

## Scheme C



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wherein  $W^2$  represents a group of the formula:  $-COOR^1$ ,  
 $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-CH(OH)CH_2OR^5$  (wherein the various  
symbols are as hereinbefore defined),  $W^3$  represents a group  
of the formula:  $-COOR^1$ ,  $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-COCH_2OR^5$   
5 (wherein the various symbols are as hereinbefore defined),  
 $W^4$  represents a group of the formula:  $-COOR^1$ ,  $-CH_2OH$ ,  
 $-CON(R^6)_2$  or  $-COCH_2OH$  (wherein the various symbols are as  
hereinbefore defined),  $Q$  represents a group of the formula  
 $O =$  or  $\begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$  and the other symbols are as hereinbefore  
10 defined, with the proviso that  $W^4$  does not represent a group  
of the formula  $-COCH_2OH$  when  $Q$  represents a group of the  
formula  $\begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ .

All of the reaction steps in Scheme C may be  
conducted by known methods.

15 For example, the decarboxylation step (a) may be  
carried out using a base such as potassium hydroxide or  
sodium hydroxide in a mixture of a lower alkanol such as  
methanol or ethanol and water, at a temperature from  
room temperature to the reflux temperature of the reaction  
20 mixture.

When  $W^1$  represents an ester group  $COOR^1$  in which  $R^1$  is other  
than hydrogen, the ester is saponified to a free carboxylic  
acid by this reaction. The free carboxylic acid may be  
esterified by known methods, if desired, for example, by  
25 diazomethane, if a methyl ester is desired, because of the  
easy purification.

The oxidation step (b) may be carried out by

using, for example;

- (1) dimethylsulfide-N-chlorosuccinimide complex, thioanisole-N-chlorosuccinimide complex, dimethylsulfide-chlorine complex or thioanisole-chlorine complex in a halogenated hydrocarbon such as chloroform, methylene chloride or carbon tetrachloride or in toluene at a temperature from 0°C to -30°C followed by treatment with triethylamine (cf. J. Amer. Chem. Soc., 94, 7586 (1972)).
- (2) using chromium trioxide-pyridine complex (e.g. Collins reagent) in a halogenated hydrocarbon such as chloroform, methylene chloride or carbon tetrachloride at a temperature from room temperature to 0°C, preferably at 0°C,
- (3) using Jones reagent below room temperature, or
- (4) using oxalyl chloride and dimethylsulfoxide in a halogenated hydrocarbon such as chloroform or methylene chloride at a temperature from -50°C to -60°C (Swern oxidation), and then treatment with triethylamine.

The step (c) to remove protecting groups, may be carried out, for example:

- (1) in an aqueous solution of an organic acid such as acetic acid, propionic acid, oxalic acid or p-toluenesulfonic acid or an aqueous solution of an inorganic acid such as hydrochloric acid or sulfuric acid at a temperature from room temperature to 75°C (preferably below 45°C), suitably in the presence of a water-miscible organic solvent, for example a lower

alkanol such as methanol or ethanol (preferably methanol) or an ether such as 1,2-dimethoxyethane, dioxan or tetrahydrofuran (preferably tetrahydrofuran).

- (2) by mild hydrolysis in the presence of an organic acid such as p-toluenesulfonic acid or trifluoroacetic acid in an anhydrous alkanol such as methanol or ethanol at a temperature from 10°C to 45°C.

The hydrolysis is preferably carried out using a mixture of hydrochloric acid, water and tetrahydrofuran, a mixture of hydrochloric acid, water and methanol, a mixture of acetic acid, water and tetrahydrofuran or a mixture of p-toluenesulfonic acid and anhydrous methanol.

In the reactions hereinbefore described to convert intermediates of general formula (I) to 6-keto-PGs, the group  $W^1$  is converted to a group  $W^4$ , via groups  $W^2$  and  $W^3$ .

The conversions for each of the groups represented by  $W^1$ ,  $W^2$ ,  $W^3$  and  $W^4$  are shown in the following Table.

	$W^1$	Step (a) →	$W^2$	Step (b) →	$W^3$	Step (c) →	$W^4$
20	COOR <sup>1</sup>		COOR <sup>1</sup>		COOR <sup>1</sup>		COOR <sup>1</sup>
	CH <sub>2</sub> OR <sup>5</sup>		CH <sub>2</sub> OR <sup>5</sup>		CH <sub>2</sub> OR <sup>5</sup>		CH <sub>2</sub> OH
	CON(R <sup>6</sup> ) <sub>2</sub>		CON(R <sup>6</sup> ) <sub>2</sub>		CON(R <sup>6</sup> ) <sub>2</sub>		CON(R <sup>6</sup> ) <sub>2</sub>
	OR <sup>7</sup>		OH		O		O
	CHCH <sub>2</sub> OR <sup>5</sup>		CHCH <sub>2</sub> OR <sup>5</sup>		CCH <sub>2</sub> OR <sup>5</sup>		CCH <sub>2</sub> OH

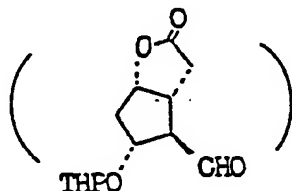
The following Reference Examples and Examples illustrate the preparation and use of compounds of the

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present invention. In the Reference Examples and Examples, 'TLC', 'NMR', 'IR', and 'Mass' represent 'Thin layer chromatography', 'Nuclear magnetic resonance spectrum', 'Infrared absorption spectrum' and 'Mass spectrum', respectively. The solvents in parentheses specified in chromatographic separations show the eluents or the developing solvents used. Except when specified otherwise, infrared absorption spectra were recorded by the liquid film method and nuclear magnetic resonance spectra were recorded in deuteriochloroform ( $\text{CDCl}_3$ ) solution.

The starting materials may be prepared by the Wittig reaction of a known compound, i.e. 2-oxa-6-syn-formyl-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo-[3,3,0]octan-3-one:

15



to introduce each  $\omega$ -chain. The reaction is hereinbefore described in published applications from (A) to (D) and therefore only the physical characteristics of each starting material are shown in the Examples below.

#### Example 1

20 (E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)oct-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

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Under an atmosphere of argon 3.4 ml of diisopropylamine was added to 30 ml of dry toluene, the mixture was cooled to 0°C and with stirring 14.5 ml of n-butyllithium was added thereto. After the mixture was

5 stirred for 30 minutes at 0°C, it was then cooled to -78°C and 5.00 g of (E)-2-oxa-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-oct-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one(starting material) in 70 ml of dry toluene was added dropwise thereto during about 30 minutes.

10 The mixture was stirred for 30 minutes at -78°C and then 2.15 g of 5-methoxycarbonylvaleryl chloride [CH<sub>3</sub>OCO(CH<sub>2</sub>)<sub>4</sub>COCl] in 10 ml of dry toluene was added thereto. After the reaction mixture obtained was stirred for 1 hour at -78°C, a mixture of water : tetrahydrofuran (0.5 ml : 5 ml) was added

15 thereto and the mixture was warmed to room temperature and then concentrated under reduced pressure to give 6.5 g of the title diketone derivative having the following physical characteristics:

TLC (ethyl acetate: n-hexane = 2 : 1) : R<sub>f</sub> = 0.41;

20 NMR :  $\delta$  = 5.6 - 5.2 (2H, m), 5.0 (1H, m),

4.62 (2H, bs), 4.2 - 3.2 (6H, m), 3.65 (1H, d),

3.64 (3H, s), 0.87 (3H, bt);

IR :  $\nu$  = 1765, 1740, 1720, 1640 cm<sup>-1</sup>;

MS:m/e = 494, 476, 463, 445, 374, 348.

25 Starting material : (E)-2-oxa-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)oct-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

TLC (ethyl acetate : n-hexane = 1 : 2) : R<sub>f</sub> = 0.38;

NMR :  $\delta$  = 5.6 - 5.3 (2H, m), 5.1 - 4.8 (1H, m),  
 4.8 - 4.5 (2H, m), 4.2 - 3.2 (6H, m),  
 2.8 - 2.0 (6H, m), 2.0 - 1.0 (20H, m),  
 0.88 (3H, t);

5 IR :  $\nu$  = 2930, 2870, 1775  $\text{cm}^{-1}$ .

By the same procedure as described in Example 1, the following compounds (a), (b), (c), (d) and (e) were obtained.

Example 1 (a)

(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

10 TLC (ethyl acetate : n-hexane = 1 : 2) :  $R_f$  = 0.47 ;

NMR :  $\delta$  = 5.6 - 5.2 (2H, m), 5.0 (1H, m),  
 4.62 (2H, bs), 4.2 - 3.2 (6H, m),  
 3.65 (1H, d), 3.64 (3H, s),  
 15 0.88 (6H, m);

IR :  $\nu$  = 1765, 1740, 1720, 1640  $\text{cm}^{-1}$ ;

MS:m/e = 522, 504, 491, 420.

Starting material : (E)-2-oxa-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

20 TLC (ethyl acetate : n-hexane = 1 : 2) :  $R_f$  = 0.37 ;

NMR :  $\delta$  = 5.6 - 5.1 (2H, m), 5.1 - 4.8 (1H, m),  
 4.8 - 4.6 (2H, m), 4.3 - 4.0 (2H, m),

4.0 - 3.7 (2H, m), 3.7 - 3.3 (2H, m),

2.9 - 2.4 (3H, m), 2.4 - 2.0 (3H, m),

2.0 - 1.0 (21H, m), 1.0 - 0.8 (6H, m);

IR :  $\nu$  = 2930, 1775  $\text{cm}^{-1}$ ;

5 MS:m/e = 380, 363, 362, 278.

Example 1 (b)

(E,E)-2-oxa-4RS-(5-methoxycarbonylpent-4-enoyl)-6-syn-[3 $\alpha$ -

(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-

(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

TLC (ethyl acetate : cyclohexane = 1 : 1) :  $R_f$  = 0.54 ;

10 NMR :  $\delta$  = 6.94 (1H, m), 5.86 (1H, bd),

5.4 - 5.65 (1H, m), 5.3 (1H, m),

5.0 (1H, m), 4.7 - 6.55 (2H, m),

3.62 (3H, s), 0.89 (6H, m);

IR :  $\nu$  = 1762, 1118, 1658, 973  $\text{cm}^{-1}$ ;

15 MS:m/e = 520, 502, 489, 471, 436, 418, 400, 374.

Starting material : the same compound as used in Example 1 (a)

Example 1 (c)

(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -

(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)but-1-enyl]-7-anti-

(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

20 NMR :  $\delta$  = 7.3 - 6.5 (4H, m), 5.6 - 5.2 (2H, m),

5.0 (1H, m), 4.6 (4H, m),

4.2 - 3.2 (6H, m), 3.65 (1H, d), 3.64 (3H, m);

IR :  $\nu$  = 1770, 1740, 1720, 1640, 1595, 1580  $\text{cm}^{-1}$ ;

MS:m/e = 566, 564, 548, 546, 535, 533.

25 Starting material : (E)-2-oxa-6-syn-[3 $\alpha$ -(tetrahydropyran-2-

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yloxy)-4-(3-chlorophenoxy)but-1-enyl]-7-anti-  
 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]  
 octan-3-one

NMR :  $\delta$  = 7.3 - 6.6 (4H, m), 5.60 (2H, m),

5            4.90 (1H, m), 4.65 (2H, m),

4.5 - 3.3 (6H, m);

IR :  $\nu$  = 1775, 1595, 1580  $\text{cm}^{-1}$ ;

MS:m/e = 508, 506, 424, 222.

Example 1 (d)

(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -  
 10 (tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-  
 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

NMR :  $\delta$  = 5.6 - 5.2 (2H, m), 4.95 (1H, m),

4.62 (2H, bs), 4.2 - 3.2 (6H, m),

3.65 (4H, s), 0.88 (3H, bt);

15 IR :  $\nu$  = 1770, 1740, 1720, 1640  $\text{cm}^{-1}$ ;

MS:m/e = 548, 530, 517.

Starting material : (E)-2-oxa-6-syn-[3 $\alpha$ -(tetrahydropyran-2-  
 yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-  
 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]  
 20 octan-3-one

TLC (ethyl acetate : n-hexane = 1 : 3) :  $R_f$  = 0.29 ;

NMR :  $\delta$  = 4.65 (2H, m), 4.06 (1H, m),

4.0 - 3.68 (3H, m), 3.58 - 3.22 (2H, m),

3.5 (2H, m), 2.95 (1H, m), 0.88 (3H, t);

IR :  $\nu$  = 2940, 2850, 1775, 1460, 1440,  
 1435, 1380, 1350, 1320, 1310,  
 1260, 1200, 1180, 1160, 1130,  
 1075, 1030, 1020, 975  $\text{cm}^{-1}$ ;

5 MS:m/e = 406, 388, 365, 304, 286,  
 281, 229, 197, 174, 123.

Example 1 (e)

(E)-2-oxa-4RS-[6RS-acetoxy-6-(2,4-dioxa-3-methylhexyl)-hexanoyl]-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

10 NMR :  $\delta$  = 5.6 - 5.2 (2H, m), 5.00 (1H, m),  
 4.6 (4H, m), 4.2 - 3.2 (12H, m),  
 2.10 (3H, s), 1.32 (3H, d),  
 1.21 (3H, d), 0.88 (3H, br);

IR :  $\nu$  = 1765, 1740, 1720, 1640  $\text{cm}^{-1}$ ;

15 MS:m/e = 644, 584, 500.

Starting material : the same compound as used in Example 1 (d)

Example 2

(E)-2-oxa-4RS-[6-(tetrahydropyran-2-yloxy)-hexanoyl]-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one

20 Under an atmosphere of argon, 14.5 ml of n-butyl lithium was added to a mixture of 0.34 ml of diisopropylamine and 5 ml of dry toluene at 0°C with stirring. The mixture was cooled to -78°C and

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490 mg of (E)-2-oxa-6-syn[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S  
-ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo  
[3.3.0]octan-3-one (starting material) in 5 ml of dry toluene  
was added thereto. After the mixture was stirred for 30  
5 minutes at the same temperature, 276 mg of 6-(tetrahydropyran-  
2-yloxy)caproic acid methyl ester in 3 ml of dry toluene was  
added thereto. The mixture was then stirred for 1 hour at the  
same temperature and then warmed to room temperature. After  
1 hour water was added to the reaction mixture and the mixture  
10 was then neutralized with oxalic acid and extracted with ethyl  
acetate. The extract was washed with water and a saturated  
aqueous solution of sodium chloride and dried and concentrated  
under reduced pressure. The residue was purified by column  
chromatography on silica gel (n-hexane : ethyl acetate =  
15 2 : 1) to give 380 mg of the title compound having the  
following physical characteristics :

TLC (n-hexane : ethyl acetate = 2 : 1) : R<sub>f</sub> : = 0.41;

NMR :  $\delta$  = 5.6-5.2 (2H, m), 5.00 (1H, m), 4.62 (3H, m),

3.60(1H, d, J=3Hz);

20 IR :  $\nu$  = 1770, 1745, 1650 cm<sup>-1</sup>;

MS:m/e = 586, 502.

Starting material : the same compound as used in Example 1 (d)

#### Reference Example 1

(13E)-(9 $\alpha$ ,11 $\alpha$ ,15S)-6-oxo-9-hydroxy-11,15-bis

(tetrahydropyran-2-yloxy)prost-13-enoic acid

25 100 ml of a mixture of water and methanol (1 : 1) and 10 ml of 5 M

aqueous solution of potassium hydroxide were added to 6.5 g of the diketone derivative prepared in Example 1 and the mixture was refluxed for 2 hours. After cooling to room temperature, an aqueous solution of oxalyl chloride was added to the reaction mixture and after the mixture was adjusted to pH 5, it was extracted with ethyl acetate and the extract was concentrated under reduced pressure to give 6.8 g of the title compound having the following physical characteristic :

TLC (ethyl acetate) : Rf = 0.36.

10 By the same procedure as described in Reference Example 1, the following compounds (a), (b), (d), (e) and (f) were obtained.

Reference Example 1 (a)

(13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,17S)-6-oxo-9-hydroxy-11,15-bis

(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid

15 TLC (ethyl acetate) : Rf = 0.33.

Starting material : (E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one (prepared in Example 1 (a))

Reference example 1 (b)

(2E, 13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,17S)-6-oxo-9-hydroxy-11,15-bis

(tetrahydropyran-2-yloxy)-17,20-dimethylprost-2,13-dienoic acid

TLC (ethyl acetate) : Rf = 0.20..

Starting material : (E,E)-2-oxa-4RS-(5-methoxycarbonylpent-4-enyl)-

6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$   
 -methylnon-1-enyl]-7-anti-  
 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]  
 octan-3-one (prepared in Example 1 (b))

Reference Example 1 (d)

5 (13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,16S,18S)-6-oxo-9-hydroxy-11,15-bis  
 (tetrahydropyran-2-yloxy)-16,18-ethano-20-ethylprost-13-enoic acid  
 TLC (ethyl acetate) : R<sub>f</sub> = 0.21.

Starting material : (E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-  
 syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-  
 10 ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-  
 yloxy)-cis-bicyclo[3.3.0]octan-3-one

(prepared in Example 1 (d))

Reference Example 1 (e)

(13E)-(1RS,9 $\alpha$ ,11 $\alpha$ ,15S,16S,18S)-1-(2,4-dioxa-3-  
 methylhexyl)-1,9-dihydroxy-6-oxo-11,15-bis(tetrahydropyran-2-yloxy)  
 15 -16,18-ethano-20-ethylprost-13-ene

TLC (ethyl acetate : cyclohexane = 1 : 1) : R<sub>f</sub> = 0.09;

NMR :  $\delta$  = 5.5 (1H, m), 5.3 (1H, m),

4.7 - 4.4 (6H, m), 4.1 - 3.2 (12H, m),

1.18 (3H, t), 0.87 (3H, m);

20 IR :  $\nu$  = 3470, 1710, 1132, 1018, 976 cm<sup>-1</sup>.

Starting material : (E)-2-oxa-4RS-[6RS-acetoxy-6-(2,4-dioxa-3-  
 methylhexyl)-hexanoyl]-6-syn-[3 $\alpha$ -  
 (tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-  
 enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-

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bicyclo[3,3,0]octan-3-one (prepared in  
Example 1 (e))

Reference Example 1 (f)

(13E)-(11 $\alpha$ , 15S, 16S, 18S)-1,11,15-tris(tetrahydropyran-2-yloxy)-  
6-oxo-9 $\alpha$ -hydroxy-16,18-ethano-20-ethylprost-13-ene

5 TLC (cyclohexane : ethyl acetate = 1 : 1) : R<sub>f</sub> = 0.38;

NMR :  $\delta$  = 5.7 - 5.2 (2H, m), 4.8 - 4.5 (3H, m), 0.89 (3H, m);

IR :  $\nu$  = 3450, 1710 (weak), 1020, 985 cm<sup>-1</sup>;

MS:m/e = 644, 558, 545, 475, 459, 440.

Starting material: (E)-2-oxa-4RS-[6-(tetrahydropyran-2-yloxy)-  
10 hexanoyl]-6-syn-[3 $\alpha$ -(tetrahydropyran-2-  
yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-  
(tetrahydropyran-2-yloxy)-cis-bicyclo-  
[3.3.0] octan-3-one (prepared in Example 2)

Reference Example 1 (c)

(13E)-(9 $\alpha$ , 11 $\alpha$ , 15S)-6-oxo-9-hydroxy-11,15-bis (tetrahydropyran-  
15 2-yloxy)-16-(3-chlorophenoxy)-17,18,19,20- tetranorprost-  
13-enoic acid methyl ester

TLC (ethyl acetate : cyclohexane = 1 : 2) : R<sub>f</sub> = 0.15;

NMR :  $\delta$  = 7.38 - 6.70 (4H, m), 5.75 - 5.46 (2H, m),

3.67 & 3.66 (3H, each s);

20 IR :  $\nu$  = 2945, 1740, 1720, 1590, 1580 cm<sup>-1</sup>.

Starting material : (E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-  
syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4-(3-  
chlorophenoxy)but-1-enyl]-7-anti-  
(tetrahydropyran-2-yloxy)-cis-bicyclo-

[3.3.0] octan-3-one (prepared in Example 1 (c)).

The starting material was decarboxylated by the procedure described in Reference Example 1 and the free carboxylic acid obtained was then esterified using diazomethane.

Reference Example 2

5 (13E)-(11 $\alpha$ ,15S)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)-prost-13-enoic acid

6.8 g of the 6-oxo-9-hydroxy derivative prepared in Reference Example 1 was dissolved in 100 ml of acetone, the mixture was cooled to -25°C and with stirring 1 ml of Jones reagent was  
10 added thereto; after 5, 10, 30, 40 and 60 minutes, 1 ml of Jones reagent was added thereto and the mixture was then stirred for an hour at the same temperature. 3 ml of isopropyl alcohol was added to the reaction mixture, the mixture was warmed to room temperature, 200 ml of water was added thereto  
15 and the mixture was extracted with ethyl acetate (200 ml x 1 time, 100 ml x 2 times).

The extract was dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 3 : 7  $\rightarrow$  4 : 6) to give 3.00 g  
20 of the title compound having the following physical characteristics:

TLC (diethyl ether) : R<sub>f</sub> = 0.36;

NMR :  $\delta$  = 5.7 - 5.3 (2H, m), 4.8 - 4.6 (2H, m),  
4.3 - 3.95 (2H, m) 3.95 - 3.7 (2H, m),  
25 3.6 - 3.4 (2H, m) 2.9 - 2.2 (9H, m),  
1.9 - 1.4 (18H, m), 1.4 - 1.1 (6H, m),  
0.86 (3H, t);

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MS:m/e = 434, 350, 332.

By the same procedure as described in Reference Example 2, the following compounds (a), (b), (c), (d), (e) and (f) were obtained.

Reference Example 2 (a)

(13E)-(11 $\alpha$ ,15S,17S)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid

TLC (ethyl acetate : n-hexane = 1 : 1) : R<sub>f</sub> = 0.09;

NMR :  $\delta$  = 5.7 - 5.3 (2H, m), 4.8 - 4.6 (2H, m),

4.3 - 4.0 (2H, m), 4.0 - 3.7 (2H, m),

3.7 - 3.3 (2H, m), 2.8 - 2.6 (3H, m),

2.6 - 2.2 (7H, m), 1.9 - 1.1 (25H, m),

1.0 - 0.8 (6H, m);

IR :  $\nu$  = 2930, 1740, 1715 cm<sup>-1</sup>;

MS:m/e = 462, 445, 378.

Starting material : (13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,17S)-6-oxo-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid (prepared in Reference Example 1 (a))

Reference Example 2 (b)

(2E,13E)-(11 $\alpha$ ,15S,17S)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprosta-2,13-dienoic acid

TLC (ethyl acetate) : R<sub>f</sub> = 0.28;

NMR :  $\delta$  = 8.0 (1H, bs), 7.0 (1H, m), 5.8 (1H, d),

5.5 (2H, m), 4.7 (2H, m), 3.7 - 4.4 (4H, m),

3.3 - 3.6 (2H, m), 0.9 (6H, m);

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Starting material : (2E,13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,17S)-6-oxo-  
 9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-  
 17,20-dimethylprost-2,13-dienoic acid  
 (prepared in Reference Example 1 (b))

Reference Example 2 (c)

5 (13E)-(11 $\alpha$ ,15S)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)-  
 16-(3-chlorophenoxy)-17,18,19,20-tetranorprost-13-enoic acid methyl  
 ester

TLC (ethyl acetate : cyclohexane = 1 : 2) :  $R_f$  = 0.31;

IR :  $\nu$  = 1750, 1720, 1590, 1580  $\text{cm}^{-1}$ ;

10 NMR :  $\delta$  = 7.30 - 6.56 (4H, m), 5.83 - 5.47 (2H, m),  
 4.90 - 4.56 (2H, m), 3.58 (3H, s).

Starting material : (13E)-(9 $\alpha$ ,11 $\alpha$ ,15S)-6-oxo-9-  
 hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-  
 16-(3-chlorophenoxy)-17,18,19,20-  
 15 tetranorprost-13-enoic acid methyl ester  
 (prepared in Reference Example 1 (c))

Reference Example 2 (d)

(13E)-(11 $\alpha$ ,15S,16S,18S)-6,9-dioxo-11,15-bis (tetrahydropyran-  
 2-yloxy)-16,18-ethano-20-ethylprost-13-enoic acid :

TLC (ethyl acetate) :  $R_f$  = 0.46;

20 MS:m/e = 488, 404, 386, 279.

Starting material : (13E)-(9 $\alpha$ ,11 $\alpha$ ,15S,16S,18S)-6-oxo-9-hydroxy  
 -11,15-bis(tetrahydropyran-2-yloxy)-  
 16,18-ethano-20-ethylprost-13-enoic acid  
 - (prepared in Reference Example 1 (d))

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Reference Example 2 (e)

(13E)-(11 $\alpha$ ,15S,16S,18S)-1-(2,4-dioxa-3-methylhexyl)-1,6,9-trioxo-11,15-bis-(tetrahydropyran-2-yloxy)-16,18-ethano-20-ethylprost-13-ene

TLC (ethyl acetate : cyclohexane = 1 : 1) : R<sub>f</sub> = 0.36;

5 NMR :  $\delta$  = 5.6 (1H, m), 5.4 (1H, m), 4.83 (3H, m),

4.78 (1H, q), 4.8 - 4.6 (2H, m),

4.7 - 4.4 (4H, m), 4.2 - 4.0 (1H, m),

4.09 (2H, d), 1.34 (3H, d), 1.19 (3H, t),

0.88 (3H, t);

10 IR :  $\nu$  = 1743, 1715, 973 cm<sup>-1</sup>;

MS:m/e = 575, 546, 529, 472, 444, 426, 421, 418, 400.

Starting Material : (13E)-(1RS,9 $\alpha$ ,11 $\alpha$ ,15S,16S,18S)-

1-(2,4-dioxa-3-methylhexyl)-1,9-dihydroxy-6-

oxo-11,15-bis(tetrahydropyran-2-yloxy)-16,18-

15 ethano-20-ethylprost-13-ene (prepared in

Reference Example 1 (e))

Reference Example 2 (f)

(13E)-(11 $\alpha$ ,15S,16S,18S)-1,11,15-tris(tetrahydropyran-2-yloxy)-6,9-

dioxo-16,18-ethano-20-ethylprost-13-ene

TLC (cyclohexane : ethyl acetate = 2 : 1) : R<sub>f</sub> = 0.24;

20 NMR :  $\delta$  = 5.8 - 5.2 (2H, m), 4.85 - 4.5 (3H, m), 0.89 (3H, m);

IR :  $\nu$  = 1743, 1710, 1032, 974 cm<sup>-1</sup>;

MS:m/e = 558, 474, 456, 390, 372, 354.

Starting material : (13E)-(11 $\alpha$ ,15S,16S,18S)-1,11,15-

tris(tetrahydropyran-2-yloxy)-6-oxo-9 $\alpha$ -

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hydroxy-16,18-ethano-20-ethylprost-13-ene

(prepared in Reference Example 1 (f) )

Reference Example 3(13E)-(11 $\alpha$ ,15S)-6,9-dioxo-11,15-dihydroxyprost-13-enoic acid(6-keto-PGE<sub>1</sub>)

- 5 3.0 g of 11,15-bis(tetrahydropyran-2-yloxy) derivative prepared in Reference Example 2 was dissolved in a mixture of 50 ml of acetic acid, water and tetrahydrofuran (65 : 35 : 10) and the mixture was stirred for 10 minutes at 80°C. After cooling the reaction mixture with ice, 300 ml of water was added, and the mixture
- 10 was extracted with ethyl acetate (500 ml x 1 time, 150 ml x 2 times). The extract was washed with water and a saturated aqueous solution of sodium chloride, dried and concentrated under reduced pressure to give 3.2 g of crude product. The crude product was purified by column chromatography on silica gel (ethyl acetate :
- 15 n-hexane (1 : 1)  $\rightarrow$  ethyl acetate  $\rightarrow$  methanol : ethyl acetate (1 : 5) to give 1.65 g of the title compound having the following physical characteristics :
- TLC (1% acetic acid / ethyl acetate) : R<sub>f</sub> = 0.36;
- Melting point : 67 - 69°C;
- 20 NMR :  $\delta$  = 5.7 - 5.5 (2H, m), 4.8 - 4.2 (3H, br),  
 4.2 - 4.0 (2H, m), 2.85 - 2.6 (2H, m),  
 2.6 - 2.3 (7H, m), 1.7 - 1.4 (6H, m),  
 1.4 - 1.2 (6H, m), 0.87 (3H, t);
- IR(CHCl<sub>3</sub>):  $\nu$  = 3400, 2940, 1745, 1715 cm<sup>-1</sup>;
- 25 MS:m/e = 368(M<sup>+</sup>), 350, 332.

By the same procedure as described in Reference Example 3, the following compounds (a), (b), (c), (d), (e), (f) and (g) were obtained.

Reference Example 3 (a)

(13E)-(11 $\alpha$ ,15S,17S)-6,9-dioxo-11,15-dihydroxy-17,20-  
5 dimethylprost-13-enoic acid

TLC (1% acetic acid / ethyl acetate) : R<sub>f</sub> = 0.36;

NMR :  $\delta$  = 5.56 (2H, m), 4.2 - 4.0 (2H, m),

4.3 - 3.6 (3H, br), 2.9 - 2.6 (3H, m),

2.6 - 2.3 (7H, m), 1.7 - 1.5 (4H, m),

10 1.5 - 1.1 (9H, m), 0.9 (6H, m);

IR :  $\nu$  = 3350, 2920, 1735, 1710 cm<sup>-1</sup>;

MS:m/e = 378, 360.

Starting material : (13E)-(11 $\alpha$ ,15S,17S)-6,9-dioxo-11,15-  
bis(tetrahydropyran-2-yloxy)-17,20-  
15 dimethylprost-13-enoic acid (prepared in  
Reference Example 2 (a))

Reference Example 3 (b)

(2E, 13E)-(11 $\alpha$ , 15S, 17S)-6,9-dioxo-11,15-dihydroxy-17,20-  
dimethylprost-2,13-dienoic acid

NMR :  $\delta$  = 6.97 (1, dt), 5.80 (1H, d), 5.55 (2H, m),

20 4.6 - 3.8 (7H, m), 2.79 (1H, dd), 0.89 (6H, m);

IR :  $\nu$  = 3600 - 2400, 1740, 1705, 1654, 973 cm<sup>-1</sup>;

MS:m/e = 376, 358, 306, 277, 259, 249, 231.

Starting material : (2E,13E) -(11 $\alpha$ ,15S,17S)-6,9-dioxo-  
11,15-bis(tetrahydropyran-2-yloxy)-17,20-

- 35 -

dimethylprost-2,13-dienoic acid (prepared  
in Reference Example 2 (b))

Reference Example 3 (c)

(13E)-(11 $\alpha$ ,15S)-6,9-dioxo-11,15-dihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranorprost-13-enoic acid methyl ester

5 TLC (ethyl acetate) : R<sub>f</sub> = 0.42;

NMR :  $\delta$  = 7.31 - 6.72 (4H, m), 5.82 - 5.66 (2H, m),

4.60 - 4.40 (1H, m), 4.30 - 3.85 (5H, m),

3.65 (3H, s), 2.98 - 2.15 (10H, m),

1.68 - 1.45 (4H, m);

10 IR :  $\nu$  = 2950, 2880, 1740, 1715, 1590, 1580 cm<sup>-1</sup>.

Starting material : (13E)-(11 $\alpha$ ,15S)-6,9-dioxo-11,15-bis  
(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)  
-17,18,19,20-tetranorprost-13-enoic acid  
methyl ester (prepared in Reference Example

15 2 (c))

Reference Example 3 (d)

(13E)-(11 $\alpha$ ,15S,16S,18S)-6,9-dioxo-11,15-dihydroxy-16,18-ethano-20-ethylprost-13-enoic acid

TLC (ethyl acetate) : R<sub>f</sub> = 0.087;

Melting point : 76 - 79°C;

20 NMR :  $\delta$  = 5.57 (2H, m), 4.09 (1H, m), 3.83 (1H, m),

2.78 (1H, dd), 0.88 (3H, m);

IR(KBr method):  $\nu$  = 3600 - 2400, 1747, 1728, 1708, 973 cm<sup>-1</sup>;

MS:m/e = 404, 386, 279.

Starting material : (13E)-(11 $\alpha$ ,15S,16S,18S)-6,9-dioxo-

11,15-bis(tetrahydropyran-2-yloxy)-16,18-ethano-20-ethylprost-13-enoic acid (prepared in Reference Example 2 (d))

Reference Example 3 (e)

(13E)-(11 $\alpha$ ,15S,16S,18S)-1-hydroxymethyl-1,6,9-trioxo-11,15-  
5 dihydroxy-16,18-ethano-20-ethylprost-13-ene [(16S,18S)-2-decarboxy-2-glycoloyl-16,18-ethano- $\omega$ -dihomo-6-keto-PGE<sub>1</sub>]

TLC (ethyl acetate : formic acid = 80 : 1) : R<sub>f</sub> = 0.21;

Melting point : 95 - 96°C;

NMR :  $\delta$  = 5.60 (2H, m), 4.24 (2H, s), 4.12 (1H, m),  
10 3.86 (1H, m), 2.79 (1H, mdd), 0.88 (3H, m);

IR(KBr method):  $\nu$  = 3460, 1748, 1732, 1710, 1288, 970 cm<sup>-1</sup>.

MS:m/e = 418, 400, 382, 369, 293, 257, 229.

Starting material : (13E)-(11 $\alpha$ ,15S,16S,18S)-1-(2,4-dioxo-3-methylhexyl)-1,6,9-trioxo-11,15-bis  
15 (tetrahydropyran-2-yloxy)-16,18-ethano-20-ethylprost-13-ene (prepared in Reference Example 2 (e))

Reference Example 3 (f)

(13E)-(11 $\alpha$ ,15S,16S,18S)-1,11,15-trihydroxy-6,9-dioxo-16,18-ethano-20-ethylprost-13-ene [(16S,18S)-2-decarboxy-2-  
20 hydroxymethyl-16,18-ethano- $\omega$ -dihomo-6-keto-PGE<sub>1</sub>]

TLC (ethyl acetate : formic acid = 400 : 5) : R<sub>f</sub> = 0.18;

Melting point : 92 -95 °C;

NMR :  $\delta$  = 5.6 (2H, m), 4.10 (1H, q), 3.84 (1H, q),  
3.64 (2H, t), 2.79 (1H, dd), 2.70 (1H, m).

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0.89 (3H, t);

IR(KBr method):  $\nu = 3420, 1747, 1710, 975 \text{ cm}^{-1}$ ;

MS:m/e = 390, 372, 364, 265, 247.

Starting material : (13E)-(11 $\alpha$ ,15S,16S,18S)-1,11,15-  
 5 tris(tetrahydropyran-2-yloxy)-  
 6,9-dioxo-16,18-ethano-20-  
 ethylprost-13-ene(prepared in  
 Reference Example 2 (f) )

Reference Example 3 (g)

(13E)-(9 $\alpha$ ,11 $\alpha$ ,15S)-6-oxo-9,11,15-trihydroxyprost-13-  
 10 enoic acid (6-keto-PGF<sub>1 $\alpha$</sub> )

TLC (1% acetic acid / ethyl acetate) : R<sub>f</sub> = 0.18;

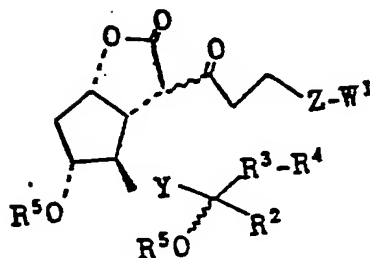
NMR (acetone-d<sub>6</sub>):  $\delta = 5.6 - 5.4$  (2H, m),  
 4.5 and 4.1 (1/2H x 2, m), 4.0 (1H, m),  
 3.8 (1H, m), 3.5 - 2.5 (4H, br),  
 15 2.9 - 2.7 (1H, m), 2.5 - 1.9 (9H, m),  
 1.8 - 1.4 (12H, m), 0.85 (3H, m);

IR(KBr method):  $\nu = 3420, 2940, 1700 \text{ cm}^{-1}$ .

Starting material : (13E)-(9 $\alpha$ ,11 $\alpha$ ,15S)-6-oxo-9-hydroxy-11,15-  
 bis(tetrahydropyran-2-yloxy)-13-enoic acid  
 20 (prepared in Reference Example 1)

CLAIMS

1. A compound of the general formula:



(I)

(wherein Y and Z, which may be the same or different, each represents a trans-vinylene group or an ethylene group,  $R^2$  represents a single bond or an alkylene group of 1 to 5 carbon atoms,  $R^4$  represents an alkyl group of 1 to 8 carbon atoms, a cycloalkyl group of 4 to 7 carbon atoms unsubstituted or substituted by at least one alkyl group of 1 to 8 carbon atoms or a phenyl or phenoxy group unsubstituted or substituted by at least one halogen atom, trifluoromethyl group or alkyl group of 1 to 4 carbon atoms,  $R^5$  represents a hydroxy-protecting group which can be removed in acidic conditions and  $W^1$  represents a group of the formula :  $-COOR^1$ ,  $-CON(R^6)_2$ ,  $-CH_2OR^5$  or  $-CH(OR^7)CH_2OR^5$  (in which  $R^1$  represents a hydrogen atom or an alkyl group of 1 to 12 carbon atoms, the groups  $R^6$ , which may be the same or different, each represents an alkyl group of 1 to 4 carbon atoms, a phenyl group or an aralkyl group of 7 to 12 carbon atoms or  $R^7$  represents an acyl group of 2 to 12 carbon atoms and  $R^5$  is as hereinbefore defined) with the proviso that, when  $R^3$  represents a single bond,  $R^4$  does not represent a substituted

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or unsubstituted phenoxy group.

2. A compound according to claim 1 wherein  $W^1$  represents a group of the formula:  $-COOR^1$  (in which  $R^1$  represents a hydrogen atom or an alkyl group of 1 to 12 carbon atoms.)

3. A compound according to claim 1 wherein  $W^1$  represents a group of the formula:  $-CH(OR^7)CH_2OR^5$ , in which  $R^5$  and  $R^7$  are as defined in claim 1.

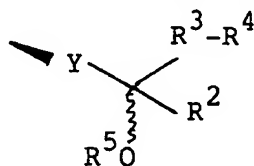
4. A compound according to claim 1, 2 or 3 wherein  $R^2$  represents a hydrogen atom and  $-R^3-R^4$  represents n-pentyl, 2-methylhexyl, (3-butyl)cyclopentyl, or (3-chlorophenoxy)-methyl.

5. A compound according to any one of the preceding claims wherein  $R^5$  represents a tetrahydropyran-2-yl group or a 1-ethoxyethyl group.

6. A compound according to any one of the preceding claims wherein Y represents trans- vinylene.

7. A compound according to any one of the preceding claims in which the  $OR^5$  group in the side chain

20



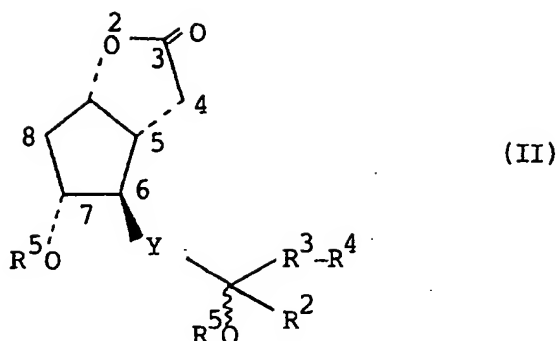
is in  $\alpha$ -configuration.

8. A compound according to claim 1 which is:

(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -

- (tetrahydropyran-2-yloxy)oct-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-  
5 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
(E,E)-2-oxa-4RS-(5-methoxycarbonylpent-4-enoyl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-5 $\alpha$ -methylnon-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)but-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
(E)-2-oxa-4RS-(5-methoxycarbonylvaleryl)-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
15 (E)-2-oxa-4RS-[6RS-acetoxy-6-(2,4-dioxa-3-methylhexyl)-hexanoyl]-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-(tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one,  
and  
(E)-2-oxa-4RS-[6-(tetrahydropyran-2-yloxy)-hexanoyl]-6-syn-[3 $\alpha$ -(tetrahydropyran-2-yloxy)-4S,6S-ethanodec-1-enyl]-7-anti-  
20 (tetrahydropyran-2-yloxy)-cis-bicyclo[3.3.0]octan-3-one.

9. Process for the preparation of a compound of general formula (I) depicted in claim 1 wherein the various symbols are as defined in claim 1 which comprises the  
25 acylation at the 4-position of a compound of the general formula:

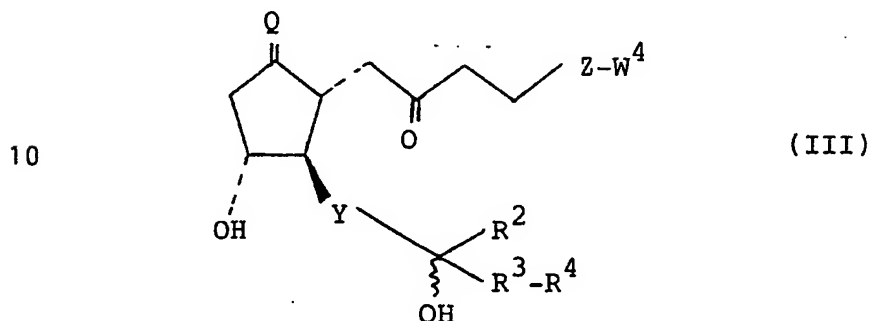


(wherein all of the symbols are as defined in claim 1) with a reactive derivative of a carboxylic acid of the general formula:




wherein all of the symbols are as defined in claim 1 to introduce the side chain  $-\text{CO}(\text{CH}_2)_2-\text{Z}-\text{W}^1$ .

10. Process for the preparation of a prostaglandin derivative of the general formula:

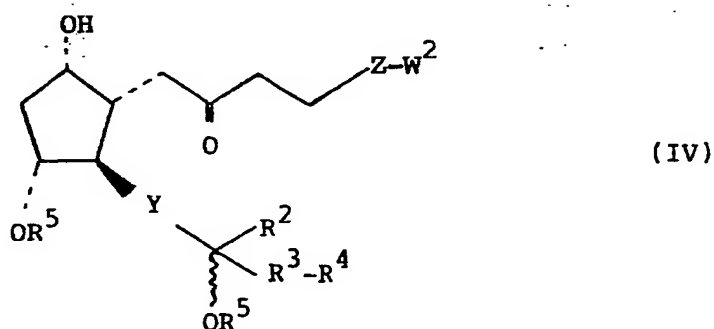


[wherein  $\text{W}^4$  represents a group of the formula:  $-\text{COOR}^1$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CON}(\text{R}^6)_2$  or  $-\text{COCH}_2\text{OH}$  (wherein the various symbols are as defined in claim 1),  $\text{Q}$  represents a group of the formula  $=\text{O}$  or  $\begin{array}{c} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H} \end{array}$  and the other symbols are as defined in claim 1, with the proviso that  $\text{W}^4$  does not represent a group of the formula  $-\text{COCH}_2\text{OH}$  when  $\text{Q}$  represents

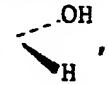
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a group of the formula  ] which process comprises:

(a) decarboxylating a compound of the general formula (I) depicted in claim 1 wherein the various symbols are as defined in claim 1, to obtain a compound of the general formula:

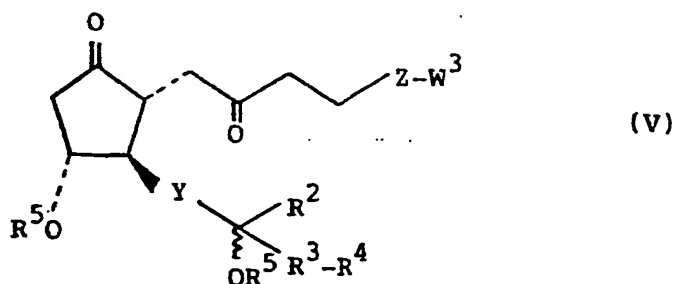


wherein  $W^2$  represents a group of the formula  $-COOR^1$ ,  $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-CH(OH)CH_2OR^5$  (wherein the various symbols are as defined in claim 1) and the other symbols are as defined in claim 1, and if desired esterifying by known methods a compound obtained in which  $W^2$  represents a group of the formula  $-COOH$ , and

(b) hydrolysing the compound of general formula (IV) to obtain a prostaglandin derivative of the general formula (III) wherein Q represents a group of the formula ,  $W^4$  is as hereinbefore defined and the other symbols are as defined in claim 1, or

(c) oxidising the compound of general formula (IV) to obtain a compound of the general formula;

20

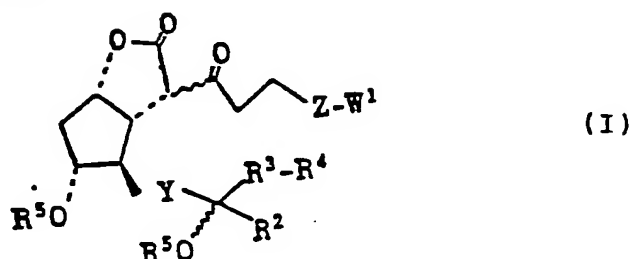


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wherein  $W^3$  represents a group of the formula  $-COOR^1$ ,  $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-COCH_2OR^5$  (wherein the various symbols are as defined in claim 1) and the other symbols are as defined in claim 1, followed by the hydrolysis of the compound 5 of general formula (V) to obtain a prostaglandin derivative of general formula (III) wherein Q represents a group of the formula  $=O$  and the other symbols are as defined in claim 1.

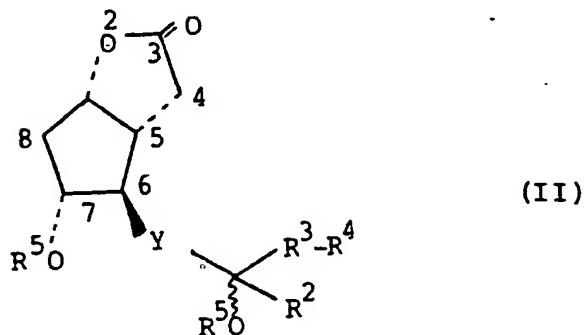
CLAIMS (AT)

1. A process for the preparation of a compound of the general formula:

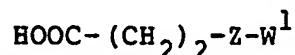


- (wherein Y and Z, which may be the same or different, each represents a trans-vinylene group or an ethylene group,  $R^2$  represents a hydrogen atom or a methyl or ethyl group,  $R^3$  represents a single bond or an alkylene group of 1 to 5 carbon atoms,  $R^4$  represents an alkyl group of 1 to 8 carbon atoms, a cycloalkyl group of 4 to 7 carbon atoms unsubstituted or substituted by at least one alkyl group of 1 to 8 carbon atoms or a phenyl or phenoxy group unsubstituted or substituted by at least one halogen atom, trifluoromethyl group or alkyl group of 1 to 4 carbon atoms,  $R^5$  represents a hydroxy-protecting group which can be removed in acidic conditions and  $W^1$  represents a group of the formula :  $-COOR^1$ ,  $-CON(R^6)_2$ ,  $-CH_2OR^5$  or  $-CH(OR^7)CH_2OR^5$  (in which  $R^1$  represents a hydrogen atom or an alkyl group of 1 to 12 carbon atoms, the groups  $R^6$ , which may be the same or different, each represents an alkyl group of 1 to 4 carbon atoms, a phenyl group or an aralkyl group of 7 to 12 carbon atoms or  $R^7$  represents an acyl group of 2 to 12 carbon atoms and  $R^5$  is as hereinbefore defined) with the proviso that, when  $R^3$  represents a single bond,  $R^4$  does not represent a substituted

or unsubstituted phenoxy group which comprises the acylation at the 4-position of a compound of the general formula:



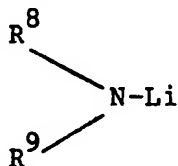
- 5 (wherein all of the symbols are as hereinbefore defined) with a reactive derivative of a carboxylic acid of the general formula:



wherein all of the symbols are as hereinbefore defined

- 10 to introduce the side chain  $-\text{CO}(\text{CH}_2)_2-\text{Z}-\text{W}^1$ .

2. A process according to claim 1 in which the selective acylation at the 4-position is carried out by reacting the compound of general formula II with a lithium compound of the general formula:



15

(wherein  $\text{R}^8$  and  $\text{R}^9$ , which may be the same or different, each represents an alkyl group of 1 to 6 carbon atoms or a cycloalkyl group of 3 to 6 carbon atoms) or an alkali metal alkoxide or alkali metal bis(trialkyl-

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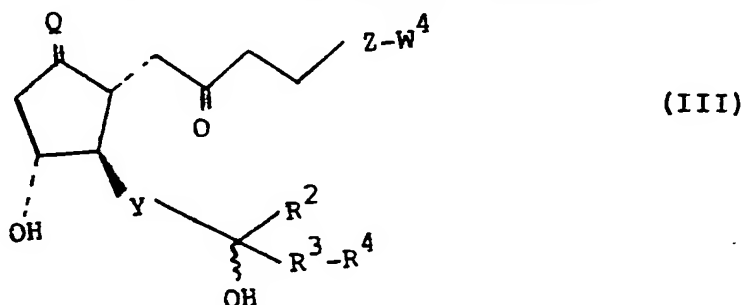
silyl)amide in an inert organic solvent at a temperature from -78°C to room temperature, followed by reaction with the reactive derivative at a temperature from -78°C to room temperature.

3. A process according to claim 2 in which the compound of general formula II is reacted with lithium diisopropylamide.

4. A process according to claim 1, 2 or 3 in which the reactive derivative of the compound of formula  $\text{HOOC}-(\text{CH}_2)_2-\text{Z}-\text{W}^1$  is an acid halide, acid anhydride, or a diester compound (in which  $\text{W}^1$  represents  $-\text{COOR}^1$  and  $\text{R}^1$  is other than hydrogen) or a mixed acid anhydride.


5. A compound according to claim 4 in which the reactive derivative is an acid chloride.

6. Process for the preparation of a prostaglandin derivative of the general formula:




[wherein  $\text{W}^4$  represents a group of the formula:  $-\text{COOR}^1$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CON}(\text{R}^6)_2$  or  $-\text{COCH}_2\text{OH}$  (wherein the various

symbols are as defined in claim 1), Q represents a

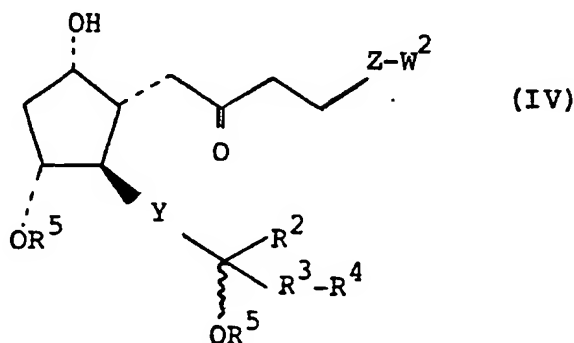
group of the formula = O or  and the other

5 symbols are as defined in claim 1, with the proviso that  $W^4$  does not represent a group of the formula

$-COCH_2OH$  when Q represents a group of the formula  ]

10 which process comprises:

(a) decarboxylating a compound of the general formula (I) depicted in claim 1 wherein the various symbols are as defined in claim 1, to obtain a compound of the general formula:



15

wherein  $W^2$  represents a group of the formula  $-COOR^1$ ,  $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-CH(OH)CH_2OR^5$  (wherein the various symbols are as defined in claim 1) and the other symbols are as defined in claim 1, and if desired

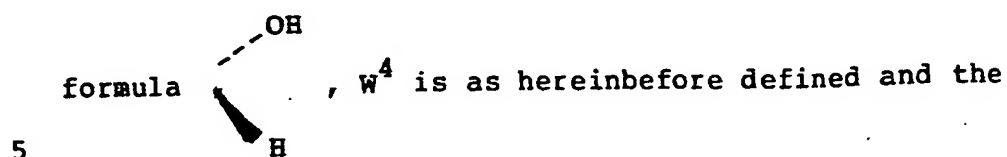
20 esterifying by known methods a compound obtained in

which  $W^2$  represents a group of the formula  $-COOH$ , and

(b) hydrolysing the compound of general formula (IV) to

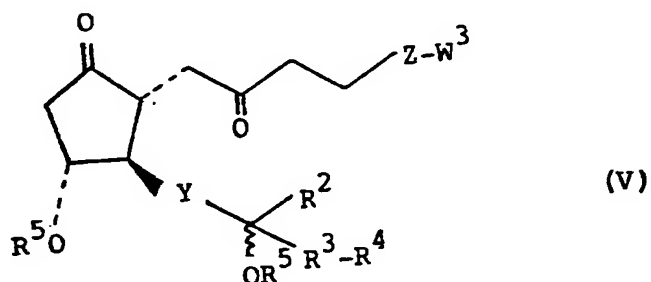
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obtain a prostaglandin derivative of the general  
 formulal (III) wherein Q represents a group of the



other symbols are as defined in claim 1, or

(c) oxidising the compound of general formula (IV) to  
 obtain a compound of the general formula:



10 wherein  $W^3$  represents a group of the formula  $-COOR^1$ ,  
 $-CH_2OR^5$ ,  $-CON(R^6)_2$  or  $-COCH_2OR^5$  (wherein the various  
 symbols are as defined in claim 1) and the other  
 symbols are as defined in claim 1, followed by the  
 hydrolysis of the compound of general formula (V) to  
 15 obtain a prostaglandin derivative of general formula  
 (III) wherein Q represents a group of the formula  $=O$   
 and the other symbols are as defined in claim 1.

7. A process according to claim 6 in which the  
 decarboxylation is carried out using a base in a  
 20 mixture of a lower alkanol and water, at a temperature  
 from room temperature to the reflux temperature of the  
 reaction mixture.

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